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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/821,203	04/09/2004	David Sidransky	001107.00463	9884

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EXAMINER	
CANELLA, KAREN A	
ART UNIT	PAPER NUMBER
1643	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/821,203	SIDRANSKY ET AL.	
	Examiner	Art Unit	
	Karen A. Canella	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-14,23 and 24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) *1-10 and 23* is/are allowed.

6)☐ Claim(s) *11* is/are rejected.

7)☐ Claim(s) *12-14* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/9/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

After review and reconsideration, the finality of the Office action of July 11, 2007 is withdrawn.

Claims 1-14, 23 and 24 are pending and under consideration.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 11-14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for identifying mutations at nucleotide 1796 if the digested products contain one fragment fewer compared to digested products formed when using wild type BRAF as a template for amplifying and digesting,, does not reasonably provide enablement for identifying mutations at nucleotide 1796 if the digested products contain one additional fragment compared to digested products formed when using wild type BRAF as a template for amplifying and digesting. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The instant claims require in part the use of TspR1 restriction endonuclease to form a digested product of double stranded DNA, in order to detect a T to A transversion in said DNA at nucleotide 1796. The art teaches that the A to T transition creates a new recognition site for TspR1, thus the T to A mutation would cause a loss of a recognition site for said TspR1 enzyme and result in one fragment fewer than the number of fragments evident from the digestion of wild type DNA without the T to A transversion. Thus, it is unclear how a T to A transversion could provide for an additional fragment when using the TspR1 enzyme as required by the claims as said transversion results in a loss of a TspR1 restriction site. One of skill in the art would be subject to undue experimentation without reasonable expectation of success in order to practice the broadly claimed method.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 11 is rejected under 35 U.S.C. 103(a) as being unpatentable over Morris et al (WO 03/08583) in view of Sidransky (WO95/19448), Shaag et al (BBRC, 1997, Vol. 233, pp. 637-639) and the New England Biolabs On-line Catalog (1998-1999).

Claim 11 is drawn to a method for detecting a T to A transversion mutation at nucleotide 1796 of BRAF (SEQ ID NO:1) comprising amplifying part of exon 15 of BRAF from a test sample to form amplified products wherein said part comprises at least nucleotides 1792 to 1799 of BRAF; digesting the amplified products with restriction endonuclease TspR1 to form digested products; identifying a mutation at nucleotide 1796 if the digested products contain one fragment fewer than digested products formed when using wild type BRAF as a template from amplifying or digesting.

Morris et al teach a method for the detection of oncogenic mutations, comprising the steps of : (a) isolating a first sample of cellular material from a naturally-occurring tissue of a subject which is suspected to be cancerous, and a second sample of cellular material from a non-cancerous tissue of the same subject; (b) examining nucleic acid material from at least part of one or more B-raf genes in both said samples of cellular material; and (c) determining whether such nucleic acid material comprises one or more point mutations in a sequence encoding a RAF polypeptide; and said mutation being present in the naturally-occurring cellular material from the suspected cancerous tissue but not present in the cellular material from the non-cancerous tissue wherein . wherein the point mutation is T1796A in B-raf. (Table 86). Morris et al teach that amplification of the target nucleic acids by PCR is within the scope of the invention (page 14, line 39 to page 15, line 1). Morris et al do not specifically teach using RFLP to identify the T1796A in B-raf

Shaag et al teach the TspR1 restriction endonuclease as useful for detecting an A to T transition mutation (abstract).

The New England Biolabs Catalog teaches that the recognition site for the TspR1 endonuclease is NNCA(C/G)TGNN.

Sidransky teaches the detection of any neoplastic target nucleic acid sequence of diagnostic or therapeutic relevance, wherein the target sequence includes a mutation resulting in a restriction fragment length polymorphism (page 8, line 23 to page 9, line 5). Sidransky teaches mutant oncogenes such as p53 and ras as target nucleic acids of diagnostic and therapeutic relevance (page 9, lines 15-20).

It would have been prima facie obvious at the time the claimed invention was made to use the TspR1 enzyme to detect the mutant T1796A of BRAF by RLFP using TspR1, wherein the presence of T1796A would be evidence by detecting one fewer fragment relative to wild type BRAF nucleic acids. One of skill in the art would have been motivated to do so by the teachings of Sidransky et al on the use of RFLP in the detection of a mutation within an oncogene and the teachings of the New England Biolabs Catalog on the recognition site of the TspR1 enzyme and the teachings of Shaag et al on the specific restriction endonuclease of TspR1 which is sensitive to and A to T transversion mutation. It is within the purview of one of skill in the art to compare the sequence of wild type BRAF and mutated BRAF comprising T1796A to find restriction enzyme recognitions sites that differ between the wild type and mutant BRAF.

Claim 11 is rejected under 35 U.S.C. 103(a) as being unpatentable over Davies et al (Nature, 2002, Vol. 417, pp. 949-954, reference of the IDs submitted April 9, 2004) in view of Sidransky (WO95/19448), Shaag et al (BBRC, 1997, Vol. 233, pp. 637-639) and the New England Biolabs On-line Catalog (1998-1999).

Claim 11 is drawn to a method for detecting a T to A transversion mutation at nucleotide 1796 of BRAF (SEQ ID NO:1) comprising amplifying part of exon 15 of BRAF from a test sample to form amplified products wherein said part comprises at least nucleotides 1792 to 1799 of BRAF; digesting the amplified products with restriction endonuclease TspR1 to form digested products; identifying a mutation at nucleotide 1796 if the digested products contain one

fragment fewer than digested products formed when using wild type BRAF as a template from amplifying or digesting.

Davies et al teach a method for the detection of oncogenic mutations, comprising amplifying through the coding exons and he intron-exon junctions of the BRAF gene, followed by direct sequencing of polymerase chain reaction products. Davies et al teach a V599E mutation accounting for 80% of the mutated BRAF in malignant melanoma (abstract and first paragraph). Davies et al teach that the V599E mutation corresponds to a T1796A mutation of the nucleic acid level (figure 1(b)). Davies et al do not specifically teach using RFLP to identify the T1796A in B-raf

Shaag et al teach the TspR1 restriction endonuclease as useful for detecting an A to T transition mutation (abstract).

The New England Biolabs Catalog teaches that the recognition site for the TspR1 endonuclease is NNCA(C/G)TGNN.

Sidransky teaches the detection of any neoplastic target nucleic acid sequence of diagnostic or therapeutic relevance, wherein the target sequence includes a mutation resulting in a restriction fragment length polymorphism (page 8, line 23 to page 9, line 5). Sidransky teaches mutant oncogenes such as p53 and ras as target nucleic acids of diagnostic and therapeutic relevance (page 9, lines 15-20).

It would have been prima facie obvious at the time the claimed invention was made to use the TspR1 enzyme to detect the mutant T1796A of BRAF by RLFP using TspR1, wherein the presence of T1796A would be evidence by detecting one fewer fragment relative to wild type BRAF nucleic acids. One of skill in the art would have been motivated to do so by the teachings of Sidransky et al on the use of RFLP in the detection of a mutation within an oncogene and the teachings of the New England Biolabs Catalog on the recognition site of the TspR1 enzyme and the teachings of Shaag et al on the specific restriction endonuclease of TspR1 which is sensitive to and A to T transversion mutation. It is within the purview of one of skill in the art to compare the sequence of wild type BRAF and mutated BRAF comprising T1796A to find restriction enzyme recognitions sites that differ between the wild type and mutant BRAF.

All other rejections and objections as set forth or maintained in the previous Office action are withdrawn in light of applicants Supplemental Declaration under Rule 1.131 submited September 10, 2007.

Claims 1-10, 23 and 24 are free of the art.

Claims 12-14 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 10-6:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571)272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Karen A. Canella/
Ph.D., Primary Examiner
Art unit 1643